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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/725,182 | 11/29/2000 | Jeffrey R. Ryan | 0207-0007 (WRAIR 98-41X) | 8763 |

7590 12/18/2001

Office of the Staff Judge Advocate
U.S. Army Medical Research and Materiel Command
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| EXAMINER | |
|---|---|
| BASKAR, PADMAVATHI | |
| **ART UNIT** | **PAPER NUMBER** |
| 1645 | |

DATE MAILED: 12/18/2001

/1

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/725,182 | RYAN ET AL. | |
| | Examiner | Art Unit | |
| | Padmavathi v Baskar | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 September 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 3-53* is/are pending in the application.

4a) Of the above claim(s) *9,10,21-26,28 and 30-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,3-8,11-20,27,29 and 41-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *1 and 3-53* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

***Response to Amendment***

1. The amendment filed on 9/28/01 has been entered into the record. Claims 1, 3-8, 11-20, 27 and 29 have been amended. Claim 2 has been canceled. New claims 41-53 have been added to the elected invention, said election being made in Paper # 6 (5/10/01). Claims 1, 3-8, 11-20, 27, 29 and 41-53 are currently under examination.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

***Rejection Withdrawn***

3. In view of amendment to the claim 1, the Examiner has withdrawn the rejection of claims 1, 3-8 under 35 U.S.C. 112, first paragraph rejection with regard to soluble excretory and secretory antigen.

***Rejections Maintained***

4. The rejection of claims 1, 3-8 and 41-44 under 35 U.S.C. 112, first paragraph with regard to antibody fragment thereof is maintained as set forth in the previous office action.

The rejection is based on 35 U.S.C. 112, first paragraph, because the specification, while enabling for an immunoassay for detecting antibodies in a subject comprising the steps of contacting a sample from the subject with a Leishmania soluble excretory and secretary antigen prepared by utilizing a protein free medium and detecting the presence or measuring the amount of an antibody in a sample bound to the soluble antigen does not reasonably provide an immunoassay for detecting antibodies in a subject comprising the steps of contacting a sample from the subject with a Leishmania soluble excretory and secretary antigen prepared by utilizing a protein free medium and detecting the presence or measuring the amount of antibody fragment in the sample bound to the soluble antigen as recited broadly in instant claims.

Instant claims are evaluated for scope of enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in In re Wands, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence

of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

With regard to antibody fragment, in the instant case, other than an immunoassay for detecting the presence of antibodies to Leishmania parasites, it does not provide guidance and direction for an immunoassay for detecting fragments of antibody. There is no guidance how to measure the fragments of antibodies in a sample using this assay. Further, it is noted that antibody fragments are not present in a sample to be detected by Leishmania antigen. Based on experiments with proteolytic enzymes such as papain or trypsin which cleave the immunoglobulin molecule (i.e., antibody) into two Fab (F (ab) $_2$) fragments consisting of light chain fragment and heavy chain fragment (see chapter 9, page 210, left column; Fundamentals of Immunology; edited by William Paul). This Fab portion of the molecule contains the antigen binding site activity. This type of cleavage (i.e., antibody fragment) does not occur in vivo situations to antibodies (i.e., anti-Leishamania antibodies) present in a sample. Further, It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the immunoglobulin. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc.Natl.Acad.Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Thus binding of an antigen to an antibody is critical. Therefore, altered antibody (i.e., "fragment ") would bind to the antigen as recited in the claims and requires undue experimentation. Further, one can use antibody or fragments to detect an antigen in a subject but one would not be able to detect antibody fragments in a subject.

The specification provides inadequate direction or guidance regarding how to detect fragments of antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Therefore, in view of the inadequate guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to antibodies/fragments capable of binding to soluble antigens.

This rejection is maintained for essentially the same reasons as the rejection of claims 1, 3-8 under this statutory provision, as set forth above in the last Office action. Applicants' arguments filed on 9/28/01, have been fully considered but they are not deemed to be persuasive.

Applicant argues s that the detection of antibody fragments in a sample obtained from a subject is enabled by the disclosure and may be practiced by using conventional methods in the

art. Although the antibody fragments are not generally present in a sample obtained from a subject but conventional treatment with papain or trypsin can be used to cleave the immunoglobulin molecule and cites 12 U.S.P.Q 2d 1904 (Bd.App 1989).

It is the Examiner's position that antibody fragments are not generally present in a sample, as applicant rightly pointed out and it is not routine to use proteolytic enzymes such as papain and trypsin to screen antibodies for detecting exposure to Leishmania parasites. Further, antibody fragments can be made by number ways. Different treatments with different reagents would result in different fragments (light chain, heavy chain, Fc, CDR, F (ab) 2. However, the specification neither teaches nor supports fragments (see paragraph # of the previous office action). Since antibody fragments are not generally found in the sample, the point here is whether the fragments after the conventional treatment with any proteolytic enzyme would bind to the soluble antigen or not. While treatment of antibodies with proteolytic enzymes in the art of immunology for studying humanized antibodies may be conventional but antibodies treated with enzymes for diagnostic assay's is not conventional. Further, treatment of antibodies with papain, pepsin, and reducing agent would result in different fragments. Applicants have not addressed this issue. The present assay is a diagnostic assay for detecting antibodies to Leishmania parasites but not a routine screening method for detecting antibody fragment. Therefore, this rejection is maintained.

5. The objection to the specification for failing to provide proper antecedent basis for the claimed subject matter See 37 CFR 1.75(d)(1) and MPEP § 608.01(o) is maintained. Correction of the following is required: In claim 1, "fragment" has no support in the specification.

6. The rejection of claims 1, 3-5, 7, 8 and 41-44 under 35 U.S.C. 102(b) as being anticipated by Martin et al 1998 (Annals of Tropical Medicine and Parasitology 1998, 92 (5) 571-577) is maintained as set forth in the previous office action.

Martin et al 1998 (Annals of Tropical Medicine and Parasitology July 1998, 92 (5) 571-577) disclose an immunoassay (i.e., ELISA) for detecting visceral leishmaniasis (see abstract). Promastigotes of L.donovani were cultured in protein free medium, XOM™. The spent medium was collected and centrifuged. Soluble antigen concentration was adjusted and used for coating the micro titer plates (see page 572, left column, second paragraph under preparation of ELISA plates). Test serum was diluted with PBS and dispensed into the coated wells (i.e., contacting a sample from the subject with the soluble antigen). Plates were washed and treated with goat-antihuman IgG conjugated with horseradish peroxidase. Plates were treated with substrate and the optical density of the contents of each well was read and levels of Leishmania specific IgG were detected (see figure 2). Since the Office does not have the facilities for examining and comparing applicant's protein free medium comprising D, xylose, hepes buffer, L-glutamate and sodium bicarbonate to the protein free medium of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed protein free medium and the prior art protein free medium. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594. The prior art anticipated the claimed invention.

This rejection is maintained for essentially the same reasons as the rejection of claims 1, 3-5, 7 and 8 under this statutory provision, as set forth above in the last Office action. Applicants' arguments filed on 9/28/01, have been fully considered but they are not deemed to be persuasive.

Applicant asserts "Martin et al never disclosed the oncotic agent and protein free medium XOM is not available to general public, those without permission from the inventors, as GIBCO is under a strict agreement to not disclose the ingredients of XOM or make it available to others."

It is the Examiner's position that Martin et al used the protein free medium XOM in order to culture *Leishmania* strains from KEMRI, the medium is available to the public and it works although the ingredients are not disclosed. Here, the issue is an immunoassay for detecting the antibodies. Martin et al clearly disclose such an assay, which uses the soluble antigens obtained from culturing promastigotes in protein free medium and the immunoassay works. In the absence of evidence to the contrary the protein free medium of the disclosed prior art contains oncotic agent/cross linking agent such as xylose. Since the Office does not have the facilities for examining and comparing applicant's protein free medium comprising D, xylose,

hepes buffer, L-glutamate and sodium bicarbonate to the protein free medium and the immunoassay performed utilizing the soluble antigens prepared from culturing the parasites in protein free medium of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed protein free medium and immunoassay and the prior art protein free medium and immunoassay. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594. Further applicant has not provided any probative evidentiary support to show that "Martin et al never disclosed the oncotic agent and protein free medium XOM is not available to general public, those without permission from the inventors, as GIBCO is under a strict agreement to not disclose the ingredients of XOM or make it available to others". Further, applicants discuss the ingredients of the XOM medium which contain oncotic agent. However, applicant is claiming an immunoassay and not the composition of the medium. Martin et al disclose an immunoassay for detecting visceral leishmaniasis (see abstract). Promastigotes of L. donovani were cultured in protein free medium, XOM.™ Therefore, this rejection is maintained.

7. The rejection of claims 1, 3 –8 and 41-44 under 35 U.S.C. 103(a) as being unpatentable over Martin et al as applied above and further in view of Wirtz et al 1989, Bulletin of the World Health Organization 1989, 67/5, 535-542 is maintained

Martin et al 1998 (Annals of Tropical Medicine and Parasitology July 1998, 92 (5) 571-577) teach an immunoassay (i.e., ELISA) for detecting visceral leishmaniasis (see abstract). Promastigotes of L.donovani were cultured in protein free medium, XOM™. The spent medium was collected and centrifuged. Soluble antigen concentration was adjusted and used for coating the micro titer plates (see page 572, left column, second paragraph under preparation of ELISA plates). Test serum was diluted with PBS and dispensed into the coated wells (i.e., contacting a sample from the subject with the soluble antigen). Plates were washed and treated with goat-antihuman IgG conjugated with horseradish peroxidase. Plates were treated with substrate and the optical density of the contents of each well was read and levels of Leishmania specific IgG were detected (see figure 2). However, the prior art does not teach diluting the sample in blocking buffer.

Wirtz et al teach an immunoassay for detecting circulating antibodies to Plasmodium falciparum. The prior art teaches sera were diluted in blocking buffer containing boiled casein

(see page 537, left column, lines 22-23). The use of boiled casein in blocking buffer reduced nonspecific binding (page 538, left column third paragraph). Optimum sensitivity was also achieved using boiled casein –Tween 20 blocking buffer, and by adding a solution of boiled casein to the capture antigen diluent (see page 536, left column, second and third paragraphs). Wirtz et al did not teach using the blocking buffer containing casein to dilute serum samples for detecting antibodies to Leishmania. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the immunoassay as taught by Martin et al by diluting the serum samples in blocking buffer containing boiled casein as taught by Wirtz et al with a reasonable expectation of success because it would have helped to reduce the non-specific binding of antibodies to the antigen and thereby increasing the chances of sensitivity of the assay. An artisan of ordinary skill would have been motivated in applying the teaching of Wirtz et al to Martin et al because Wirtz et al suggests that using boiled casein in blocking buffer reduced nonspecific binding (page 538, left column third paragraph). One of ordinary skill in the art would know how to use different concentrations of boiled casein in blocking buffer by titrating the concentration of boiled casein in blocking buffer for diluting serum samples. The claimed invention is prima facie obvious in view of Martin et al and Wirtz et al absent any convincing evidence to the contrary.

This rejection is maintained for essentially the same reasons as the rejection of claims 1, 3-5, 7 and 8 under this statutory provision, as set forth above in the last Office action. Applicants' arguments filed on 9/28/01, have been fully considered but they are not deemed to be persuasive.

Applicant asserts that prima facie case of obviousness has not been established and Martin et al or any cited prior art never suggested or disclosed the protein free medium comprising oncotic agent.

It is the Examiner position that Martin et al used the antigens obtained from culturing *Leishmania* strains from KEMRI in a protein free medium in an immunoassay. Problems of culturing of organisms are not relevant. Martin et al clearly disclose an immunoassay and it works. Applicant is claiming an immunoassay and Martin et al disclose an immunoassay for detecting visceral leishmaniasis (see abstract) utilizing antigens obtained from culturing promastigotes of L.donovani in protein free medium, XOM.™ In the absence of evidence to the contrary the prior art teaches an immunoassay which detects antibodies. Further applicant has not provided any probative evidentiary support to show that "Martin et al never disclosed the

oncotic agent and protein free medium XOM is not available to general public, those without permission from the inventors, as GIBCO is under a strict agreement to not disclose the ingredients of XOM or make it available to others". Therefore, this rejection is maintained.

8. The rejection of claims 45-49, 11-20, 27, 29 and 50-53 under 35 U.S.C. 103(a) as being unpatentable over Martin et al 1998 (Annals of Tropical Medicine and Parasitology 1998, 92 (5) 571-577) in view of WO 99/56755 and Wirtz et al is maintained.

Claims are directed to a kit/diagnostic device for the diagnosis of leishmaniasis in a subject comprising a substrate and a soluble antigen of either L.donovani or L.mexicana prepared by utilizing a protein-free medium packaged together for multiple or single use assays. Examiner views diagnostic device as a kit since it comprises Leishmania soluble antigens and means to detect antibody bound to the soluble antigen.
Martin et al teach an immunoassay (i.e., ELISA) for detecting visceral leishmaniasis (see abstract). Promastigotes of L.donovani were cultured in protein free medium, XOM™. The spent medium was collected and centrifuged. Soluble antigen concentration was adjusted and used for coating the micro titer plates (see page 572, left column, second paragraph under preparation of ELISA plates). Test serum was diluted with PBS and dispensed into the coated wells (i.e., contacting a sample from the subject with the soluble antigen). Plates were washed and treated with goat-antihuman IgG conjugated with horseradish peroxidase (i.e., anti-human IgG conjugate) Plates were treated with substrate and the optical density of the contents of each well was read and levels of Leishmania specific IgG were detected (see figure 2). Martin et al did not teach a kit and the blocking buffer. However, Wirtz et al teach an immunoassay for detecting circulating antibodies to Plasmodium falciparum. The prior art teaches sera were diluted in blocking buffer containing boiled casein (see page 537, left column, lines 22-23). The use of boiled casein in blocking buffer reduced nonspecific binding (page 538, left column third paragraph). Optimum sensitivity was also achieved using boiled casein –Tween 20 blocking buffer, and by adding a solution of boiled casein to the capture antigen diluent (see page 536, left column, second and third paragraphs).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to keep all the ingredients disclosed by the prior art in the form of a compact kit since kits are easy to transport and convenient to work in places (economically under developed countries) with less facilities. An artisan of ordinary skill would have been motivated in applying the art disclosed by Martin et al because kits would help in diagnosing leishmaniasis conveniently and do not require trained technical support since it comes with instructions to use. Although Martin et al did not teach that the samples are diluted in blocking buffer, it was well known in the art of immunology as evidenced by Wirtz et al (see Bulletin of the World Health Organization 1989, 67/5, 535-542) that diluting the sample in blocking buffer reduces the nonspecific binding of antibodies to antigens. Kits were well known in the art for testing or diagnosing varieties of parasitic diseases including the one disclosed by the prior art (WO 99/56755, claim 24). The instructions of the kit were also known as taught by WO 99/56755, claim 24. Moreover, instructions are printed matter which have been long been held to distinguish a claimed structure over the prior art only where the printed matter functions in

cooperation with the structure. Here there is no such functional cooperation between the printed instructions and the kit's structural components.

The claimed invention is prima facie obvious in view of Martin et al, Wirtz et al and WO 99/56755 absent any convincing evidence to the contrary.

This rejection is maintained for essentially the same reasons as the rejection of claims 1, 3-5, 7 and 8 under this statutory provision, as set forth above in the last Office action. Applicants' arguments filed on 9/28/01, have been fully considered but they are not deemed to be persuasive.

Applicant asserts that prima facie case of obviousness has not been established and Martin et al or any cited prior art never suggested or disclosed the protein free medium comprising oncotic agent.

It is the Examiner position that Martin et al used the antigens obtained from culturing *Leishmania* strains from KEMRI in a protein free medium in an immunoassay. Problems of culturing of organisms are not relevant. Martin et al clearly disclose an immunoassay and it works. Applicant is claiming an immunoassay and Martin et al disclose an immunoassay for detecting visceral leishmaniasis (see abstract) utilizing antigens obtained from culturing promastigotes of L.donovani in protein free medium, XOM.™ In the absence of evidence to the contrary the prior art teaches an immunoassay which detects antibodies. Further applicant has not provided any probative evidentiary support to show that "Martin et al never disclosed the oncotic agent and protein free medium XOM is not available to general public, those without permission from the inventors, as GIBCO is under a strict agreement to not disclose the ingredients of XOM or make it available to others". Therefore, this rejection is maintained.

***Status of Claims***

9. No claims are allowed.

***Conclusion***

10. This application contains claims 9-10, 21-26, 28 and 30-40 drawn to an invention

nonelected with traverse in Paper No. 6. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma Baskar whose telephone number is (703) 308-8886. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4 PM EST

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Padma Baskar Ph.D.

12/5/01

MARK NAVARRO
PRIMARY EXAMINER